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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/750,373
Filing Date: December 28, 2000
Appellant(s): LIND ET AL.

Gwilym John Owen Attwell
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/17/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1, 7-1, 12-25 and 29-33 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Skolnick, J. "From Genes to Protein Structure and Function: Novel Applications of Computational Approaches in the Genomic Era" Trends in Biotech., vol18, no. 1 (2000), pp. 34-39

Bork, P. "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle" Genome Research, vol10 (2000), pp. 398-400

Doerks, T., et al. "Protein Annotation: Detective Work for Function Prediction" Trends in Genetics, vol14, no 6 (June 1998), pp. 248-250

Smith, T.F., et al. "The Challenges of Genome Sequence Annotation or "The Devil is in the Details", Nature Biotechnology, vol15, (Nov 1997), pp. 1222-1223

Brenner, S.E. "Errors in Genome Annotation" Trends in Genetics, vol15, no. 4 (April 1999), pp. 132-133

Bork, P., et al. "Go Hunting in Sequence Databases but Watch out for the Traps" Trends in Genetics, vol12, no. 10 (Oct 1996), pp. 425-427

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A. Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 7-1, 12-25 and 29-33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility. These claims are directed to nucleic acids of SEQ ID NO:12 and which encode, or are homologous to, SEQ ID NO:25. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated protein. However, the instant application does not disclose a specific and substantial biological role of this protein or its significance.

It is clear from the instant specification that the claimed receptor is what is termed an "orphan receptor" in the art. The instant application does not disclose the biological role of the claimed protein or its significance. Appellants disclose in the specification that the claimed receptor is believed to be a G protein-coupled receptor. However, the basis that the receptor of the present invention is a 7 transmembrane, GPCR is not predictive of a use. There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Appellants' claimed invention is incomplete.

The instant situation is directly analogous to that of which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation.

However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which required that an invention must have either an immediate obvious or fully disclosed "real-world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility," "[u]nless and until a process is refined and developed to this point - where specific benefit exists in currently available form – there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

The specification discloses that the polynucleotides of the invention encode proteins which are believed to be GPCRs. However, no comparison to any known GPCR could be found in the specification. Furthermore, even if the specification asserted that the disclosed proteins have biological activities similar to known GPCRs, this cannot be accepted in the absence of supporting evidence, because generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases.

For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene.

Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a

small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan the utility of the claimed polynucleotide of SEQ ID NO:12 and the protein of SEQ ID NO:25, which are only believed to be GPCRs. Therefore, the instant claims are drawn to a polynucleotide encoding a protein which has a yet undetermined function or biological significance. There is no actual and specific significance which can be attributed to said protein identified in the specification. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real-world" use for said protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

Furthermore, since the nucleic acids of the invention are not supported by a specific and substantial asserted utility or a well established utility, the vector, host cell, polypeptide and method for producing the claimed polypeptide also lack utility.

B. Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7-1, 12-25 and 29-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(11) Response to Argument

A. Claim Rejections - 35 USC § 101

Appellants argue that the claimed invention does have a credible, substantial and specific utility (i.e. real-word use) since it can be used to identify ligands and/or protein binding partners and that the polypeptides of the invention can be used to produce antibodies which can be used to localize the protein. Appellants further argue that being able to identify specific tissue types in the CNS can also aid in the identification of CNS defects and abnormalities. Appellants also argue that they need only provide a "substantial likelihood" of utility and that GPCRs have a well-established utility since many medically significant biological processes are mediated by signal transduction pathways involving G proteins and other second messengers and that GPCRs are recognized as important therapeutic targets for a wide range of diseases.

These arguments have been considered, but are not deemed persuasive. Hundreds of proteins, especially those of the G protein-coupled family of receptors, to which this protein is alleged to belong, can be used to produce antibodies, screen for ligands, or to identify diseases. Regarding using the protein to identify ligands, this asserted utility is credible. However, it is not substantial, nor specific to the protein of the present invention. The specification does not characterize the polypeptide encoded by the polynucleotide of the claimed invention. Therefore binding sites, etc. are not identified. Significant further experimentation would be required of the skilled artisan to characterize the protein and search for ligands. There is no disclosure, for example, of how to assay for ligand binding and possible transduction mechanisms. It is not known the class of drugs to use or what measurements to perform. Since this asserted utility is not presented in mature form so it could be readily used in a real world sense, the asserted utility is not substantial. Since numerous proteins can be used in these general assays, these uses are not specific to the protein of the invention.

Regarding the production of antibodies, this asserted utility is credible, but not specific nor substantial. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, both the polypeptide and its antibodies have no patentable utility. Regarding the identification of CNS disorders, or that GPCRs are used for therapeutic agents, these asserted utilities are credible, but neither specific nor substantial. The specification does not disclose any function, nor any dysfunction, associated with altered levels or forms of the polynucleotide or polypeptide of the claimed invention. Significant further experimentation would be required of the skilled artisan to identify a dysfunction or disease associated with the claimed polynucleotide or polypeptide. There is no disclosure, for example, of any symptoms associated with such a disease or dysfunction of the

polypeptide. Since this asserted utility is not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not specific nor substantial. For the above reasons, Appellants have not demonstrated a "substantial likelihood" of utility, or that the invention has a "real-world" use.

Appellants further argue that all of the utilities described in the application are based on sound logic which is not inconsistent with the logic underlying the assertion that the polypeptides are useful and that the Office has provided no evidence that the logic is seriously flawed. These arguments have also been considered, but are also not deemed persuasive. Respectfully, the issue here is not that the logic regarding the asserted utility is flawed, since many proteins, in general, can be used to generate antibodies, to identify ligands, etc. The issue at hand is that Appellants have not provided a specific and substantial utility *for the protein of the present invention*. Appellants disclose in the specification that the claimed receptor is believed to be a G protein-coupled receptor. However, the basis that the receptor of the present invention is a 7 transmembrane, GPCR is not predictive of a use. There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Appellants' claimed invention is incomplete.

Appellants further argue that Brenner et al. (PNAS) teaches that the probability that the claimed polypeptide is related to the reference polypeptide is very high and that none of the reference cited by the Examiner contradicts Brenner's basic rule. Appellants' points regarding these references have been considered. Taken as a whole, these references show that prediction of novel proteins based on known homologous proteins is, at best, speculative. Even, *arguendo*, Brenner's rule was correct, Appellants have not identified to which protein(s) the protein of the present invention is related, nor, as argued on pages 3-5 of the Office Action dated 2/6/03, would this homology alone be sufficient to provide a utility of the present invention. If Appellants have support for specific identification of the protein, or polynucleotides, of the present invention as belonging to a specific subfamily of GPCRs, for example opioids or adrenergics, as well as specific assays further characterizing these proteins as such, they are required to point out exactly where in the specification this support can be found.

Appellants further argue In re Folkers. However, *In re Folkers* is concerned with the utility of a genus of *chemical compounds*, whereas the present invention is concerned with receptor *proteins*. Therefore, this issue is not relevant in this situation as follows. If Appellants were claiming that the protein of the present invention, or nucleic acids encoding these proteins, could be used as chemical compounds, then this argument may be relevant. However, whereas a genus of specific chemical compounds may have a utility, this is not analogous to a genus of receptors, in this case the entire

superfamily of GPCRs, having a utility. For example, the LSD-like class of indoles may be used to better understand psychiatric disorders. However, this does not suggest that all compounds that have an indole nucleus will have the same or any utility. The same situation holds true for GPCRs. Whereas if Appellants have identified the GPCR of the present invention as belonging specifically to, for example, the opioid subfamily genus of GPCRs then, based on the art's knowledge of opioid pharmacology, the protein of the present invention would be expected to have a similar utility (analogous to the LSD compounds). However, this generalization cannot be extrapolated to a GPCR with a yet unknown function (e.g. indoles in general), as Appellants are attempting to do in the present situation. The GPCR family has too many variants to be considered a genus on the same level that Appellants are arguing *In re Folkers*.

Appellants bring to the Examiner's attention numerous patents claiming GPCRs with no natural substrate or specific biological significance. This argument has been considered, but is not persuasive. First, this application was properly examined under, and is consistent with, the current utility guidelines, published 1/5/01, 66 FR 1092. Furthermore, all U.S. Patent are presumed valid, or would not have issued as U.S. Patents.

Appellants further argue that the polypeptide of the present invention is homologous to GPRA and VVR1. Appellants argue that the Examiner failed to read the specification and that the specification does teach the use of this polypeptide in the treatment of asthma. The Examiner points out that the specification is 121 pages in length and discloses numerous proteins and Appellants have not pointed out where exactly in the specification the asserted utility for the presently claimed protein can be found. The Examiner has found on pages 99-100 of the specification a laundry list of asserted utilities including:

Expression of nGPCR-1007 in these tissues provides an indication that modulators of nGPCR activity have utility for treating metabolic diseases and disorders (e.g., type 2 diabetes, obesity, anorexia, hypertension, atherosclerosis, etc.) and thyroid disorders (e.g. thyroitoxicosis, myxoedemal; inflammatory conditions (e.g., Chron's disease, rheumatoid arthritis, autoimmune disorders, movement disorders, CNS disorders (e.g., pain including migraine, stroke, psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, depression, bipolar disorder, delirium, dementia, severe mental retardation, dyskinesias, such as Huntington's disease or Tourette's Syndrome, attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, etc.); ***among others*** (emphasis added).

Appellants' specification does not disclose that the protein of the present invention is homologous to any known proteins, including the GPRA protein, VVR1, or the conpressin 2 receptor, as argued in the Brief. Appellants' argument in the Brief that "the claimed receptor exhibits about 84% sequence identity to arginine vasopressin receptors which are involved in the 'pathogenesis of asthma and other IgE-mediated diseases' as well as diabetes" appears to have been pulled from the post-filing literature, not disclosed in the specification. As stands, the laundry list of asserted utilities disclosed in the specification does not provide a specific, substantial, or well-established utility for the protein of the present invention. The Examiner is not questioning the credibility of the present invention.

Appellants argue that the protein of the present invention contains structural motifs characteristic of arginine vasopressin receptors, including a DRY motif, proline residues, residues involved in internalization, as well as cysteines and serines. However, none of these motifs identify the receptor of the present invention as an arginine vasopressin receptor. The motifs listed are characteristic of a large number of GPCRs since these motifs are involved in functions characteristic of all GPCRs. For example, it is well-known in the art that prolines are involved in receptor folding and that serine residues are phosphorylated in order to regulate desensitization/internalization. None of the motifs argued by Appellants would allow one of ordinary skill in the art to identify the protein of the present invention as an arginine vasopressin receptor. For example, Appellants have not disclosed a vasopressin binding site.

Therefore, since the nucleic acid molecules of the invention do not possess a specific, substantial and credible asserted utility or a well established utility, the claimed expression vectors, host cells, compositions and methods of making the encoded protein, also do not possess utility. It is believed that all pertinent arguments have been addressed.

B. Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Appellants argue that the claimed invention is enabled because it has utility as argued previously. Appellants' arguments have been fully considered, but are not found to be persuasive for the reasons discussed above under 35 USC 101.

For the above reasons, it is believed that the rejections should be sustained.

ROBERT LANDSMAN
PATENT EXAMINER

Respectfully submitted,

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September 28, 2004

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